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DATA CONCERNING LINKAGE IN MICE

W. L. WACHTER

Bussey Institution

In exploiting the genetics of any plant or animal it is of great importance to breed intensively and extensively until the genetic material is exhausted. Even after the dominance or recessiveness of a certain gene has been established, there yet remain to be determined the relationships between this and other genes known to constitute the hereditary complex of that particular plant or animal. These possible relationships are allelomorphic, independent, or linked. Mendel was able to formulate certain laws of heredity from the data he obtained in his breeding experiments; but had he continued his work to include other factors he would undoubtedly have been led to predict or formulate a theory of linkage. The chromosome theory of heredity involves independent inheritance of genes which lie in different chromosomes no less than linked inheritance of those which lie in the same chromosome. It is equally important in relation to this theory to know whether two genes are linked or not linked.

A very meager amount of linkage has so far been found in mammals. Cases have thus far been observed only in rabbits, rats, and mice. In rabbits Castle (1920) has recently shown that there is a probable linkage between the factors for dilution and the English type of spotting. In rats Castle and Wright (1915), and Castle (1919), had previously shown albinism, red-eye, and pink-eye to be included in the same linkage system. In mice the genes for pink-eye and albinism were first shown to be linked by the work of Darbishire (1904), as was pointed out by Haldane, Sprunt, and Haldane (1915), who confirmed the idea by observations of their own.

A great amount of data has been obtained by breeding the house mouse. Yet a further intensive study is desirable of the mutant characters discovered, especially as regards linkage, for from such study alone can be deduced the probable localization of the genes in the chromosomes. According to Harvey (1920), the number of chromosomes in the gametes of the house mouse has been estimated by different observers at from 8 to 30, the more recent observers placing the number at from 20 to 24. One of these is probably a sex chromosome which is heterozygous in the male and homozygous in the female. In this sex chromosome is apparently located the lethal gene of the Japanese waltzing mouse reported by Little (1920). In one autosome are located the linked genes for pink-eye and albinism. In another autosome must be located the gene for agouti and its allelomorphs, non-agouti, light-bellied agouti, and yellow; to a third autosome is referred piebald spotting; to a fourth, black-eyed-white spotting; while dilution and its allelomorph, intensity, will probably have to be referred to a sixth autosomal group. Thus seven of the twenty or more chromosomes are genetically identified, leaving thirteen or more yet to be identified with visible characters or mutations yet to be discovered.

Among modifying genes in mice, Little (1915) and Dunn (1920) have shown that the "blaze" or "white-face" variation which modifies the piebald pattern is heritable. Dunn (1920) also reports a "belly-spot" to segregate independently of self and piebald, though apparent only in animals heterozygous for self and piebald. General modifying factors, increasing or decreasing the area of pigment in the black-eyed-white and piebald patterns, are also heritable. Very little is known at the present time concerning these modifying factors, and nothing about their linkage relations.

THE RELATION OF AGOUTI TO PIEBALD

Dunn's (1920) data on the cross, agouti × piebald, indicated a cross-over percentage, between the genes for agouti and piebald, of only 46.23 ± 1.20, in a total of 783 young produced by a back cross of F_1 animals to the double recessive, non-agouti piebald. This shows a deviation of 3.77 per cent. from the normal 50 per cent. value expected if the genes for agouti and piebald assort independently. This deviation is barely more than three times the probable error. The data were also taken incidentally from crosses in which the primary object was to ascertain the relationship between the genes for pink-eye and piebald. This may have influenced the final result in some way, such as less attention being placed on the discrimination of agouti. Therefore further data seemed especially desirable on this relationship.

All later crosses were made with reference only to the agouti and piebald factors. The original matings were all for coupling, the cross being agouti self × non-agouti piebald (AASS × aass). The F_1 animals were heterozygous for the two factors (AaSs). Such animals should form four classes of gametes (1) AS, (2) As, (3) aS, (4) as. If the two genes are independent, these classes should be equal in number; if linked, classes (1) and (4) should be in excess. When such F_1 animals are back crossed to the double recessive, non-agouti piebald, the distribution is obtained which is shown in Table I opposite "new data."

TABLE I

RESULTS OF A BACK CROSS BETWEEN F_1 AGOUTI SELF MICE (FROM AGOUTI SELF, AS, × NON-AGOUTI PIEBALD, as) AND NON-AGOUTI PIEBALD

		AS	As	aS	as	Total	Cross-over Per Cent.
Dunn's data	Obs.	221	179	183	200	783	46.23 ± 1.20
	Exp.	195.75	195.75	195.75	195.75		
New data	Obs.	112	102	110	108	432	49.07 ± 1.61
	Exp.	108	108	108	108		
Combined data	Obs.	333	281	293	308	1,215	47.25 ± 0.96
	Exp.	303.75	303.75	303.75	303.75		

The distribution of the new and more critical data is excellent and excludes any interpretation of linkage between the two genes A and s. The cross-over classes, consisting of agouti piebald and non-agouti self, together number 212. This is 49.07 ± 1.61 per cent. of the total number of young raised, viz., 432, and the deviation is less than one per cent. from the cross-over value expected in independent assortment, which result is well within the probable error, ± 1.61.

Combining Dunn's data with the new data gives a larger number of animals on which to base conclusions. Also, any slight deviation from the normal independent segregation due to random sampling will tend to disappear when larger numbers are involved. On the other hand, a small excess of the non-cross-over class, if it consistently appears in both sets of data, must be considered significant, should it be more than three times the probable error. The combined data are shown in the lower lines of Table I. Here the cross-over classes consist of agouti piebald and non-agouti self, and include 574 individuals. This is 47.25 per cent. of the 1,215 animals raised, and has a probable error of ± 0.96. The deviation of the cross-over value from the 50 per cent. value expected in independent assortment is 2.75 a figure within the range of three times the probable error (± 2.88). The new data and the combined data agree in showing that the two genes are independent.

The Relation of Black-eyed-white Spotting to Agouti

In this section will be presented further data on the relation of black-eyed-white spotting to agouti. It is to be expected that these genes should show no linkage. Little (1912 and 1917) demonstrated the independence of yellow in relation to black-eyed-white. Since yellow, agouti, light-bellied agouti, and non-agouti are multiple allelomorphs, black-eyed-white and agouti should show the same relation to each other as black-eyed-white and yellow. Yet no direct crosses had been made to test the

point prior to the beginning of this work, and the data obtained will, therefore, have value.

Reciprocal matings were made. In the coupling series agouti black-eyed-whites (AAWwss) were crossed with non-agouti prebalds (aawwss). Since both parents were homozygous for piebald (ss), that symbol may be omitted hereafter. The F_1 agouti black-eyed-white young (AaWw) were back-crossed to the double recessive (aaww). The distribution obtained is shown in the coupling series of Table II to the right of "new data." There is an apparent excess of black-eyed-whites and agoutis, perhaps due to random sampling and inexperienced grading of some individuals. But this excess is distributed between both the cross-over and the non-cross-over classes, which consequently are not affected, the numbers being 176, 186. This gives a cross-over percentage of 48.61 ± 1.90.

TABLE II

BACK CROSSES BETWEEN F_1 AGOUTI BLACK-EYED-WHITE MICE (AaWw) AND THE DOUBLE RECESSIVE, NON-AGOUTI PIEBALD (aaww)

Test for	Data		AW	Aw	aW	aw	Total	Cross-over Per Cent.
Coupling..	Dunn's data	Obs.	36	22	22	34	114	38.59 ± 3.96
		Exp.	28.5	28.5	28.5	28.5		
	New data...	Obs.	114	90	86	72	362	48.61 ± 1.76
		Exp.	90.5	90.5	90.5	90.5		
	Combined ..	Obs.	150	112	108	106	476	46.21 ± 1.53
		Exp.	119	119	119	119		
Repulsion .	Dunn's data	Obs.[1]	77	76	76	77	306	50.32 ± 1.92
		Exp.	76.5	76.5	76.5	76.5		
		Obs.	28	27	25	32	112	53.57 ± 3.17
		Exp.	28	28	28	28		
	New data...	Obs.	50	69	52	59	230	47.39 ± 2.21
		Exp.	57.5	57.5	57.5	57.5		
	Combined ..	Obs.	155	172	153	168	648	49.84 ± 1.32
		Exp.	162	162	162	162		
			Cross-overs		Non cross-overs			
Coupling and repulsion	Dunn's data	Obs.	258		274		532	48.49 ± 1.45
		Exp.	266		266			
	New data...	Obs.	285		307		592	48.14 ± 1.38
		Exp.	296		296			
combined	Combined ..	Obs.	543		581		1124	48.30 ± 1.00
		Exp.	562		562			

[1] The cross-over and non-cross-over classes were given as 154 and 152, respectively.

The deviation from the normal distribution is less than the probable error and therefore not significant.

In the repulsion series the genes for agouti and black-eyed-white entered separately into the F_1 zygote. When back crossed these agouti black-eyed-white young gave the distribution recorded in the repulsion series of Table II opposite "new data." Here the cross-overs number 109, and the non-cross-overs 121, whereas equal numbers are expected. This is a fair distribution for the small numbers raised. Combining the new data on the reciprocal crosses gives 285 cross-overs, or 48.14 per cent. of the 592 young raised, with a probable error of ± 1.38.

Combining Dunn's data with the new data, there are 543 and 581 animals in the cross-over and non-cross-over classes, respectively. The cross-over percentage is 48.30 ± 1.00. The deviation from the normal distribution is less than twice the probable error. The data, separately and combined, clearly show the independence of the two genes.

The Relation of Black-eyed-white Spotting to Pink-Eye

Previous work by Haldane *et al.* has shown pink-eye to be linked with albinism. Detlefsen (1916) described black-eyed-white mice carrying pink-eye, which resembled albinos, but the genes segregated in the second generation. No back-crosses were made in his experiments. No direct intensive crosses hitherto published have dealt with the possible linkage relation between these genes.

In a cross made for such a study, the genes for black-eyed-white spotting and pink-eye entered separately. Accordingly the F_1 gametes should give equal numbers of the parental non-cross-over types (WP and wp), and of the new cross-over combinations (Wp and wP), if the genes W and p are independent. If linked, they should, in the back-cross, show repulsion and the former combinations be in excess of the latter. In Table III opposite "new data" of the repulsion series is shown the dis-

tribution of the young obtained when F_1 black-eyed-whites from the above cross were mated with pink-eyed piebalds, the double recessives. The cross-over classes number 134, or 46.68 ± 1.99 per cent. of the total 281 animals raised. The deviation from the distribution expected is within the probable error and indicates independent segregation.

The reciprocal cross was also made in which the two genes entered together in the same parent. The F_1 gametes should again consist of equal numbers of two classes, WP and wp (the cross-overs), and wP and Wp (the non-cross-overs), if independent segregation occurs. If linkage is shown, the latter class should be larger. The actual distribution is shown in Table III opposite "new data" of the coupling series. The agreement with expectation is poor due to small numbers (77). But since the cross-overs exceed the non-cross-overs, it is clear that no linkage exists. The cross-over per cent. is large (59.74 ± 3.77), but the deviation is still less than three times the probable error. By combining both coupling and repulsion results recorded in the new data, a total of 358 animals is obtained, of which 180 are cross-overs. This gives a cross-over percentage of 50.27 ± 1.78. The deviation from the normal distribution is 0.27 per cent., a figure well within the probable error.

These crosses, as well as Dunn's, show consistently the independence of the black-eyed-white and pink-eye genes. Further evidence may be had by adding together the cross-over and non-cross-over classes of the two sets of data as shown in Table III. The cross-overs number 330 and constitute 51.48 ± 1.32 per cent. of the total 641 animals raised. The deviation from the expected distribution is 1.48 and not significant. The number of young raised does not equal that of other crosses, for the consistency with which these data, in agreement with Detlefsen's observations, show the independence of the two genes, warranted the discontinuance of further breeding.

TABLE III

BACK CROSS BETWEEN F_1 BLACK-EYED-WHITE, HETEROZYGOUS FOR p AND W, AND THE DOUBLE RECESSIVE, PINK-EYED PIEBALD (wwpp)

Series	Data		PW	Pw	pW	pw	Total	Cross-over Pct.
Coupling..	Dunn's data	Obs.	20	11	9	19	59	66.10 ± 4.14
		Exp.	14.75	14.75	14.75	14.75		
		Obs.	21	17	21	21	80	52.50 ± 3.76
		Exp.	20	20	20	20		
	New data...	Obs.	19	20	11	27	77	59.74 ± 3.77
		Exp.	19.25	19.25	19.25	19.25		
	Combined ..	Obs.	60	48	41	67	216	63.42 ± 2.23
		Exp.	54	54	54	54		
Repulsion .	Dunn's data	Obs.	16	21	22	23	82	52.43 ± 3.70
		Exp.	20.5	20.5	20.5	20.5		
		Obs.	18	14	12	18	62	41.90 ± 4.22
		Exp.	15.5	15.5	15.5	15.5		
	New data...	Obs.	75	62	72	72	218	47.68 ± 1.99
		Exp.	70.25	70.25	70.25	70.25		
	Combined ..	Obs.	109	97	106	113	425	47.76 ± 1.63
		Exp.	106.25	106.25	106.25	106.25		
Coupling and repulsion			Cross-overs		Non-cross-overs			
	Dunn's data	Obs.	150		133		283	53.04 ± 1.99
		Exp.	141.5		141.5			
	New data...	Obs.	180		178		358	50.27 ± 1.78
		Exp.	179		179			
	Combined ..	Obs.	330		311		641	51.48 ± 1.32
		Exp.	320.5		320.5			

SUMMARY

In agreement with the views of previous investigators, it is shown by new and conclusive experimental data that the following pairs of genes in mice assort independently and are not linked. On the chromosome hypothesis, the members of each pair are located in different chromosomes: (1) the genes for agouti (A) and for piebald spotting (s); (2) the genes for agouti (A) and for black-eyed-white spotting (W); (3) the genes for pink-eye (p) and for black-eyed-white spotting (W).

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